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A PROSPECTIVE OBSERVATIONAL STUDY ON THE SAFETY AND EFFICACY OF DAPAGLIFLOZIN IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Dr. B. E. Evangileen, *Tallari Praveen, Sania Maheen, Chitrapu Sri Satya Durga and Gali Thriveni

Pharm D, Avanthi Institute of Pharmaceutical Sciences, Gunthapally, Ranga Reddy, Hyderabad, Telangana.

***Corresponding Author: Tallari Praveen**

Pharm D, Avanthi Institute of Pharmaceutical Sciences, Gunthapally, Ranga Reddy, Hyderabad, Telangana.

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ABSTRACT

Background: Persistent elevation of blood glucose levels, known as chronic hyperglycemia, is a metabolic condition indicative of diabetes mellitus, usually the consequence of the diminished release of insulin and resistance, leading to complications like microvascular, macrovascular, DKA, and HHS issues. This prospective observational study aims to determine the safety and efficacy of dapagliflozin in T2DM patients. Dapagliflozin selectively targets sodium-glucose 2 co-transporters, offering a focused therapeutic approach. The research emphasizes real-world evidence to look into how dapagliflozin affects sugar regulation, safety profiles, prescribing patterns, patient characteristics, and adverse events. The project aims to provide practical insights into dapagliflozin's application in managing T2DM, aiding informed clinical decision-making. **Methods:** One hundred patient case records were gathered in a prospective observational study that took place for six months. Prescription patterns were examined by considering age, gender, BMI, co-morbidities, and various brands of dapagliflozin. This analysis was conducted through a patient-level survey conducted in both OP and IP hospital departments, aiming to discern the safety and efficacy of dapagliflozin. **Results:** Within the study, dapagliflozin was predominantly prescribed for individuals aged 51-70, with a majority of male patients. The prescribed doses were deemed appropriate. In a sample of 100 patients, the mean fasting plasma glucose (FPG) decreased from 170.9 mg/dL before dapagliflozin administration to 133.1 mg/dL, indicating a substantial and positive effect of circulating sugar concentrations. **Conclusion:** Throughout this research, dapagliflozin was given to individuals diagnosed with T2DM. This medication is intended to reduce elevated sugar levels in the blood. No patients reported serious adverse effects associated with the use of dapagliflozin. However, 5% of participants experienced minor side effects such as dry mouth, slightly elevated serum creatinine levels, and increased urine production.

KEYWORDS: Type 2 diabetes, Dapagliflozin, and SGLT 2.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is one of the most common metabolic disorders worldwide and its development is primarily caused by a combination of two main factors: defective insulin secretion by pancreatic β-cells and the inability of insulin-sensitive tissues to respond to insulin.[1] Insulin release and action have to precisely meet the metabolic demand; hence, the molecular mechanisms involved in the synthesis and release of insulin, as well as the insulin response in tissues must be tightly regulated. Therefore, defects in any of the mechanisms involved can lead to a metabolic imbalance that leads to the pathogenesis of T2DM.

This review analyses the key aspects of T2DM, as well as the molecular mechanisms and pathways implicated in insulin metabolism and associations between T2DM and cardiovascular pathophysiology. In this review, we describe the global trends of T2DM, the roles of major risk factors, in particular, obesity, lifestyle factors, genetic predispositions, gut dysbiosis, epigenetics and mitochondrial deregulation. We highlight physiological and molecular mechanisms leading to T2DM and its complications.

According to the World Health Organization (WHO) diabetes mellitus is a chronic, metabolic disease characterized by elevated levels of blood glucose, which leads over time to damage to the heart, vasculature, eyes, kidneys and nerves. Over 90% of diabetes mellitus cases are T2DM, a condition marked by deficient insulin secretion by pancreatic islet β-cells, tissue insulin resistance (IR) and an inadequate compensatory insulin secretory response.[2,3] Progression of the disease makes insulin secretion unable to maintain glucose homeostasis, producing hyperglycaemia. Patients with T2DM are mostly characterized by being obese or having a higher body fat percentage, distributed predominantly in the abdominal region. In this condition, adipose tissue promotes IR through various inflammatory mechanisms,

including increased free fatty acid (FFA) release and adipokine deregulation. The main drivers of the T2DM epidemic are the global rise in obesity, sedentary lifestyles, high caloric diets and population aging, which have quadrupled the incidence and prevalence of T2DM.[4,5]

The organs involved in T2DM development include the pancreas (β-cells and α-cells), liver, skeletal muscle, kidneys, brain, small intestine, and adipose tissue.[6] Evolving data suggest a role for adipokine dysregulation, inflammation, and abnormalities in gut microbiota, immune dysregulation, and inflammation have emerged as important pathophysiological factors.[7]

Epidemiological data show alarming values that predict a worrisome projected future for T2DM. According to the International Diabetes Federation (IDF), in 2019, diabetes caused 4.2 million deaths; and 463 million adults aged between 20 and 79 years old were living with diabetes, a number that will likely rise up to 700 million by 2045. Diabetes was the underlying cause of at least 720 billion USD in health expenditure in 2019. Additionally, the true disease burden of T2DM is likely an underrepresentation as 1 in 3 diabetic people were underdiagnosed, equivalent to 232 million people. The greatest number of people suffering from diabetes are aged between 40 and 59 years old. Incidence and prevalence of T2DM vary according to geographical region, with more than 80% of patients living in low-to-middle-income countries, which poses additional challenges in effective treatment. Patients with T2DM have a 15% increased risk of all-cause mortality compared with people without diabetes with cardiovascular disease (CVD) as the greatest cause of morbidity and mortality associated with T2DM.[8] The association of diabetes with increased risk of coronary heart disease (hazard ratio [HR] 2.00; 95% CI 1.83–2.19), ischaemic stroke (HR 2.27; 1.95–2.65), and other vascular disease-related deaths (HR 1.73; 1.51–1.98) has been shown in a meta-analysis.[9]

Epidemiology of T2DM is affected both by genetics and the environment. Genetic factors exert their effect following exposure to an environment characterized by sedentary behavior and high-calorie intake. Common glycaemic genetic variants for T2DM have been identified by genome-wide association studies, but these only account for 10% of total trait variance, suggesting that rare variants are important.[10] People of different ethnic origins may have different specific phenotypes that increase predisposition to clusters of CVD risk factors, including hypertension, insulin resistance, and dyslipidemia.[11]

T2DM risk factors include a complex combination of genetic, metabolic and environmental factors that interact with one another contributing to its prevalence. Although individual predisposition to T2DM due to non-modifiable risk factors (ethnicity and family history/genetic predisposition) has a strong genetic basis, evidence from epidemiological studies suggests that many cases of T2DM can be prevented by improving the main modifiable risk factors (obesity, low physical activity and an unhealthy diet).[12,13]

Globally, the incidence and prevalence of T2DM are found to vary widely depending on ethnicity and geographical region with Japanese, Hispanics and Native Americans having the highest risks.[14,15,16] It has been shown higher incidence rates in Asians compared with a White American population[17,18], and white population in the UK,[19], where the highest risk is among the black population.[20] Whilst no clear reasons have been found, contributing factors such as modern lifestyle factors (which promote obesity), socioeconomic and direct genetic propensity or gene environmental interactions have been postulated.

Genetic predisposition plays an important part in the risk of developing T2DM. Over the past decade, several T2DM genome-wide association studies have shown the complex polygenic nature of T2DM in which most of these loci increase T2DM risk through primary effects on insulin secretion, and a minority act through reducing insulin action.[21,22] Dimas et al. grouped these variants on the basis of their potential intermediate mechanisms in T2DM pathophysiology, with four variants fitting a clear IR pattern; two reducing insulin secretion with fasting hyperglycemia; nine lowering insulin secretion with normal fasting glycemia; and one altering insulin processing.[23] According to these data, the genetic architecture of T2DM is highly polygenic, and additional association studies are needed to identify most T2DM loci.[24] Interactions between susceptibility loci and environmental factors could underlie the missing heritability of T2DM thus the impact of a given genetic variant can be modulated by the environmental factors (and vice versa) as evidenced by both observational studies and clinical trials.[25]

Need for the study is T2DM, a major disease accompanied by many complications. Patient safety: It helps assess the safety profile of dapagliflozin in present clinical settings, including information on potential adverse effects associated with the medication. Efficacy of Drug: By observing Dapagliflozin's effectiveness, the study can provide medication post-marketing surveillance: Dapagliflozin is approved and in use. A prospective observational study of its performance in a heterogeneous population can help as a post-marketing surveillance process to monitor safety and efficacy in the current population.

The main aim of the project is to study the safety and efficacy of dapagliflozin in patients with T2DM.

MATERIALS AND METHODS

Study Site

The study was done at a single location, Aware Gleneagles Global Hospital, LB Nagar, Hyderabad, Telangana.

Study Design

A prospective observational study was performed.

Duration Of The Study

It was done for six months.

Sample Size

A population of 100 subjects was included in the study.

Study Criteria

Inclusion Criteria

- Those who have been diagnosed as having type 2 DM.
- Both male and female patients are included.
- Individuals who would like to give their informed consent.
- Patients who are conscious and cooperative.
- Patients from the endocrinology department

Exclusion Criteria

- Patients who have eGFR <45 ml/min/1.73m²
- Pregnant women.
- Lactating women.
- Patients who are not co-operative.
- Psychiatric patients.
- Patients with Type 1 DM.

Source Of Data

The data required for the study was collected using the patient's medical records. Data was collected from outpatient and inpatient departments and entered into collection forms.

Method Of Data Collection

- Data collection form.
- Patient prescription.
- Informed consent form.

Patient Data Collection Form

A carefully crafted patient information gathering form was created in compliance with the study's details.

Data Analysis

- Evaluated the demographic characteristics among those participating in the research, including gender, age, and baseline health status.
- We analyze side effects reported during the survey period.
- Assessed the achievement of glycemic targets among participants.
- Analyze the prescribing patterns, including the distribution of dapagliflozin formulations (e.g., Udapa, Dapefy, and Dapanorm).
- Examined the reasons behind prescribing choices, considering factors such as cost, perceived risk, and patient-specific characteristics.
- Explored the influence of co-morbidities, such as hypertension, hypothyroidism, MI, and diabetic retinopathy, on the safety and efficacy outcomes.
- Assessed whether the presence of co-morbidities affects dapagliflozin's performance.
- Employed statistical methods to identify significant associations and correlations.
- Conducted subgroup analyses to explore variations in outcomes within specific patient groups.

Statistical Analysis

The information gathered has been reviewed by the use of approximate statistical tools.

- Google Sheets

Ethical Clearance

Prior to commencing the trial, ethical clearance will be acquired from the institutional ethical committee of Aware Gleneagles Global Hospital.

RESULTS AND DISCUSSION

The study was carried out with 100 patients who were prescribed dapagliflozin in the department of endocrinology.

DISTRIBUTION OF THE STUDY POPULATION BY GENDER

In the study population, out of 100 patients, 61 are males (61%), and 39 are females (39%).

Table 1: Distribution of the study population by gender

GENDER	POPULATION	Percentage
male	61	61%
female	39	39%

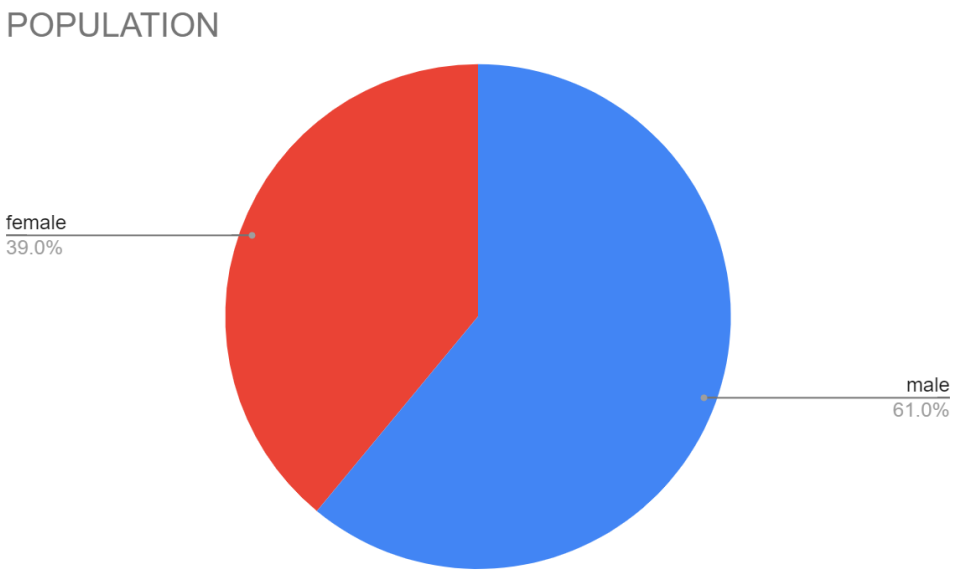

Fig. 1: Distribution of the study population by gender.

DISTRIBUTION OF THE STUDY POPULATION BY AGE

Out of 100 patients, it was observed that most of them were prescribed dapagliflozin and belonged to the age group of 30-40 years (10%), 41-50 years (14%), 51-60 years (30%), 61-70 years (31%), 71-80 years (10%), 81-90 years (5%).

Table 2: Distribution of the study population by age.

S.NO	AGE GROUP (YEARS)	NO. OF PATIENTS
1	30-40	10
2	41-50	14
3	51-60	30
4	61-70	31
5	71-80	10
6	81-90	5

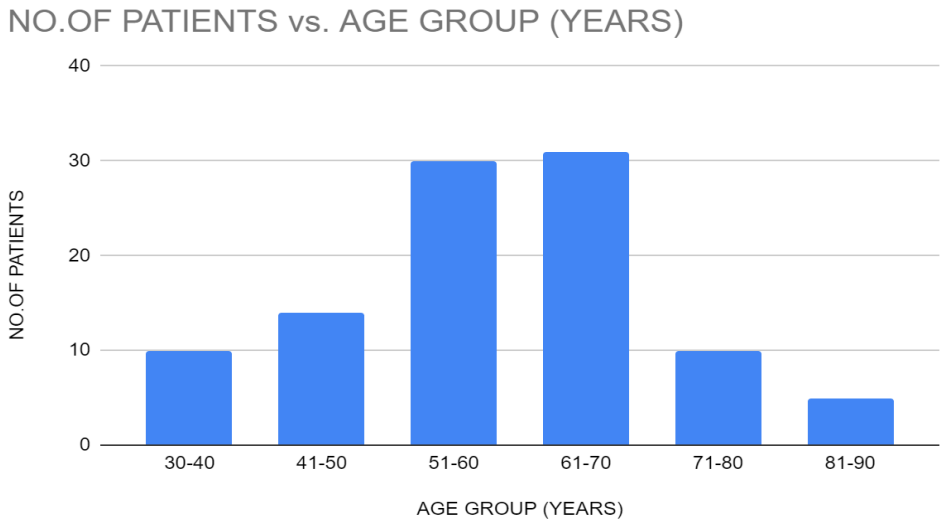

Fig. 2: Distribution of the study population by age.

POPULATION DISTRIBUTION FOR THE RESEARCH BASED ON FAMILY HISTORY

Out of 100 patients, 61% have a history of diabetes and 39% have no history of diabetes.

Table 3: Population distribution for the research based on family history.

Family history of DM	No. of patients	Percentage
Yes	61	61%
No	39	39%

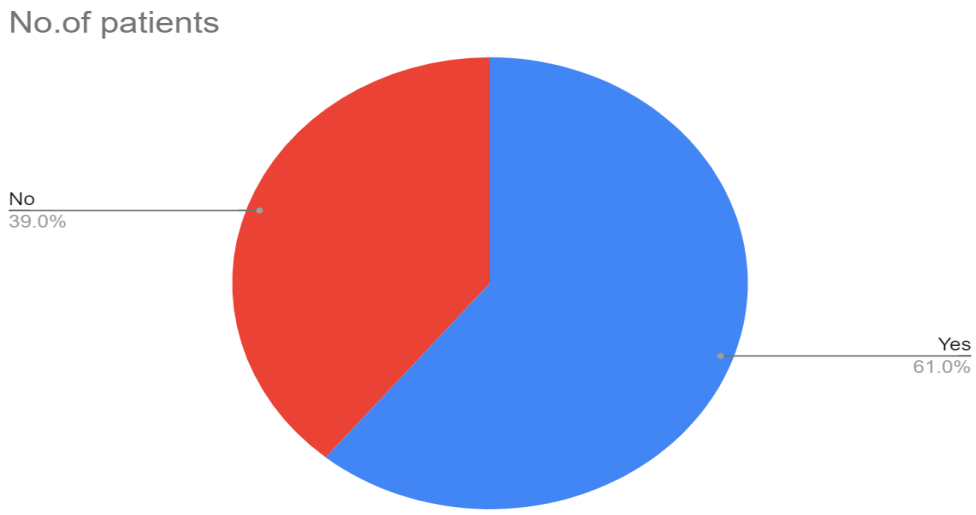

Fig. 3: Population distribution for the research based on family history.

Distribution Based On Body Mass Index

Out of 100 patients, 31 have a normal BMI, 49 are overweight, and 20 are obese.

Table 4: Distribution based on BMI.

Underweight	<18.4	0
Normal Weight	18.5 - 24.9	31
Overweight	25 - 29.9	49
Obese	30 - 40	20

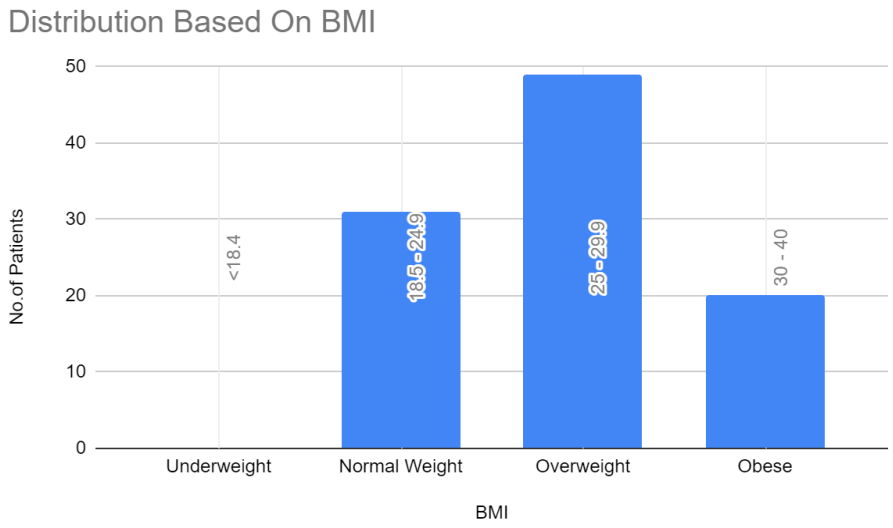

Fig. 4: Distribution based on BMI.

DISTRIBUTION BASED ON CO-MORBIDITIES:
Out of 61 male patients, 16 have co-morbidities, 11 have HTN, 2 have CAD, 1 have LV dysfunction, and 2 have hypothyroidism.

Out of 39 female patients, 11 have co-morbidities, 5 have HTN, 2 have CAD, 2 have MI, 1 have LV dysfunction, and 1 have retinopathy.

Table 5: Distribution Based On Comorbidities.

DISEASES	MALE	FEMALE
Type 2 DM	37	22
De novo DM		1
HTN + DM	11	5
CAD + DM	2	2
MI + DM		2
LV dysfunction + DM	1	1
Hypothyroidism + DM	2	
Retinopathy + DM		1

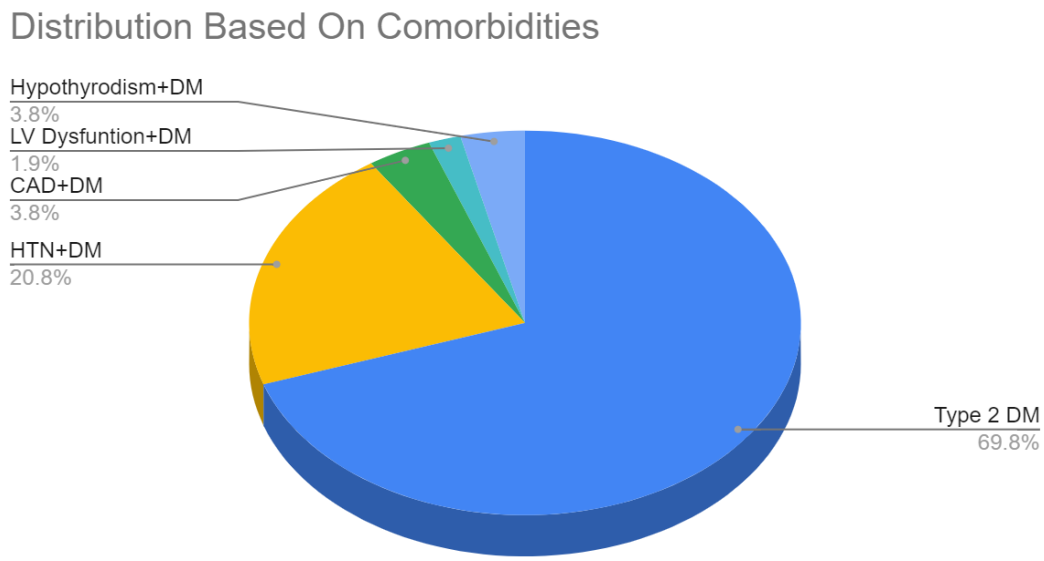

Fig. 5: Distribution Based On Comorbidities.

DISTRIBUTION BASED ON MULTIPLE CO-MORBIDITIES
Out of 61 male patients, 7 have multiple co-morbidities.
Out of 39 female patients, 5 have multiple co-morbidities.

Table 6: Distribution Based On Multiple Co-morbidities.

S.NO	DISEASE	MALE	FEMALE	TOTAL
1	Diabetic Foot Ulcer + DM + HTN	1		1
2	HTN + CAD + DM	1		1
3	HTN + Nephropathy + DM		1	1
4	HTN + Cervical Spondylitis + DM	1		1
5	HTN + Diabetic Foot Ulcer + DM		1	1
6	HTN + Retinopathy + DM	1	1	2
7	HTN + Hypothyroidism + DM		1	1
8	HTN + LV dysfuntion + DM	1		1
9	HTN + CAD + Neuropathy + DM	1		1
10	HTN + CAD + De novo DM	1		1

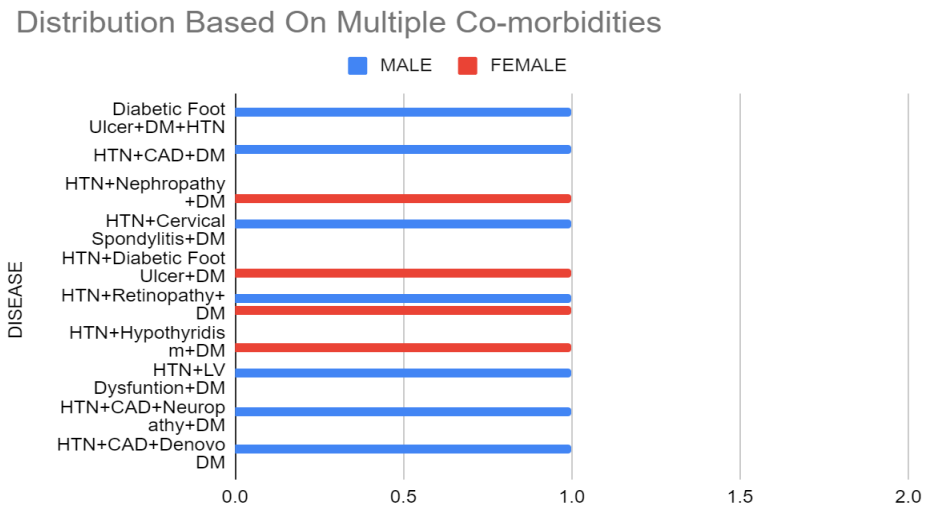

Fig. 6: Distribution Based on Multiple Co-morbidities.

DIFFERENT BRANDS OF DAPAGLIFLOZIN PRESCRIBED

Among 100 patients, 55% were prescribed with Udapa-10 mg, 25% were prescribed with Dapefy-10 mg, 11% were prescribed with Dapanorm-10 mg, 5% were prescribed with Dapasach-10 mg, and 4% were prescribed with Oxra-10 mg.

Table 7: Different brands of Dapagliflozin prescribed in the study population

S.NO	BRAND NAMES	NO.OF PATIENTS
1	Udapa-10mg	55
2	Dapefy-10mg	25
3	Dapanorm-10mg	11
4	Dapasach-10mg	5
5	Oxra-10 mg	4

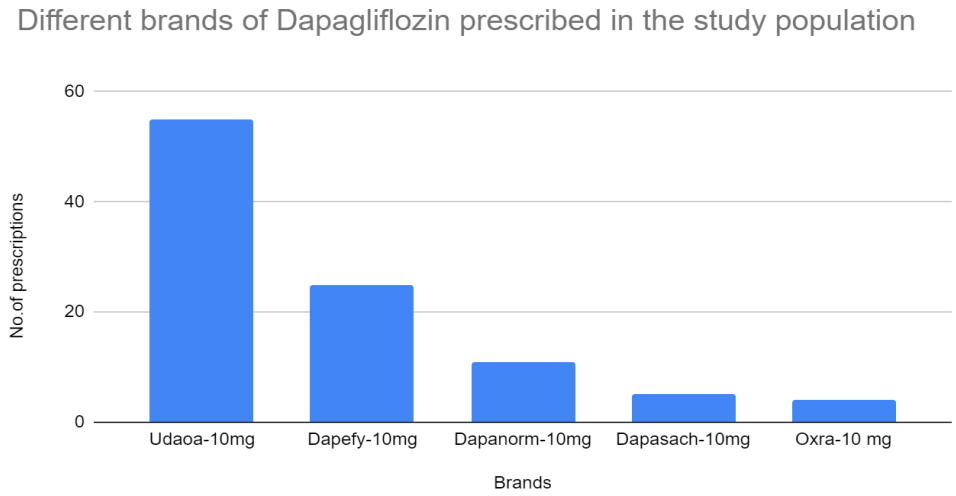

Fig. 7: Different brands of Dapagliflozin prescribed in the study population.

SAFETY

The safety results of dapagliflozin in a sample of 100 individuals are as follows.

Out of the 100 individuals.

2 experienced dry mouth.

2 had slightly elevated serum creatinine levels.

One patient reported increased urine production.

It's important to note that the remaining 95 individuals did not report any side effects. These findings provide an overview of side effects associated with dapagliflozin use, with dry mouth, slightly elevated serum creatinine levels, and increased urine production being observed in a small percentage of the sample.

Table 8: Safety Results Of Dapagliflozin.

SIDE EFFECTS	NO. OF CASES
No side effects	95
Dry mouth	2
Elevated Sr. Creatinine	2
Increased urination	1

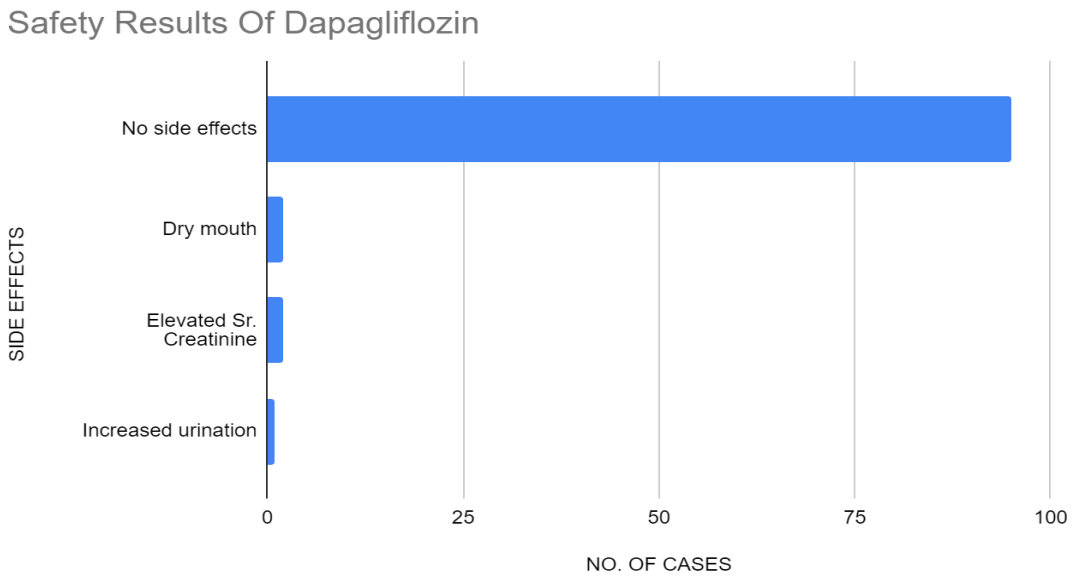

Fig. 8: Safety Results of Dapagliflozin.

EFFICACY

The efficacy of the drug dapagliflozin is predominantly evaluated through the measurement of FPG levels, which serve as a crucial indicator. Before the administration of dapagliflozin, the mean FPG was 170.9 mg/dL in a sample of 100 patients. Following the use of dapagliflozin, the mean FPG showed a decrease to 133.1 mg/dL. This reduction in the mean FPG strongly indicates a favorable impact of dapagliflozin on glucose levels.

Table 9: Mean of FPG before and after use of Dapagliflozin.

Use Of Dapagliflozin	FPG Mean
Before	170.9
After	113.1

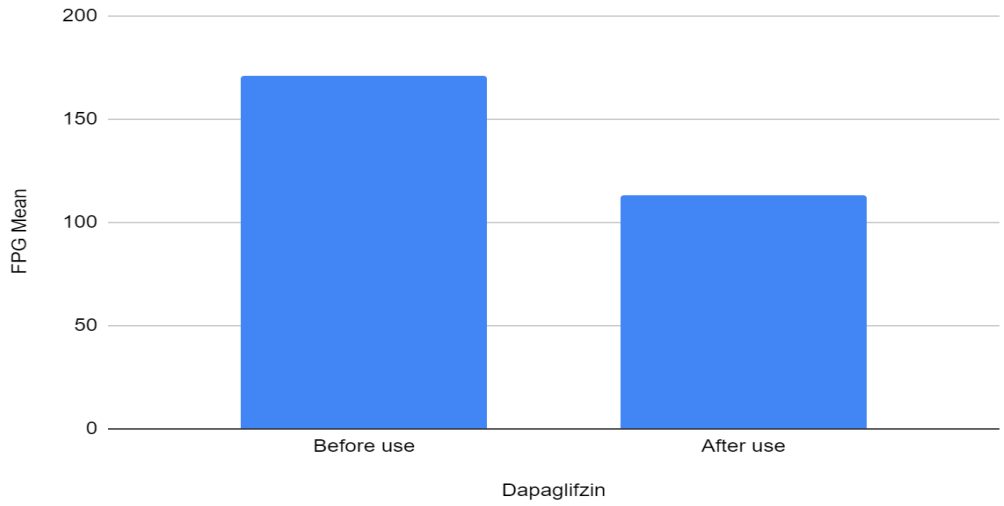

Fig. 9: Mean of FPG before and after use of Dapagliflozin.

INDICATION ACCURACY

Table 10: Indication Accuracy.

INDICATION	NO.OF CASES	P-VALUE
Appropriate	100	
Inappropriate	0	P>0.001
Total	100	

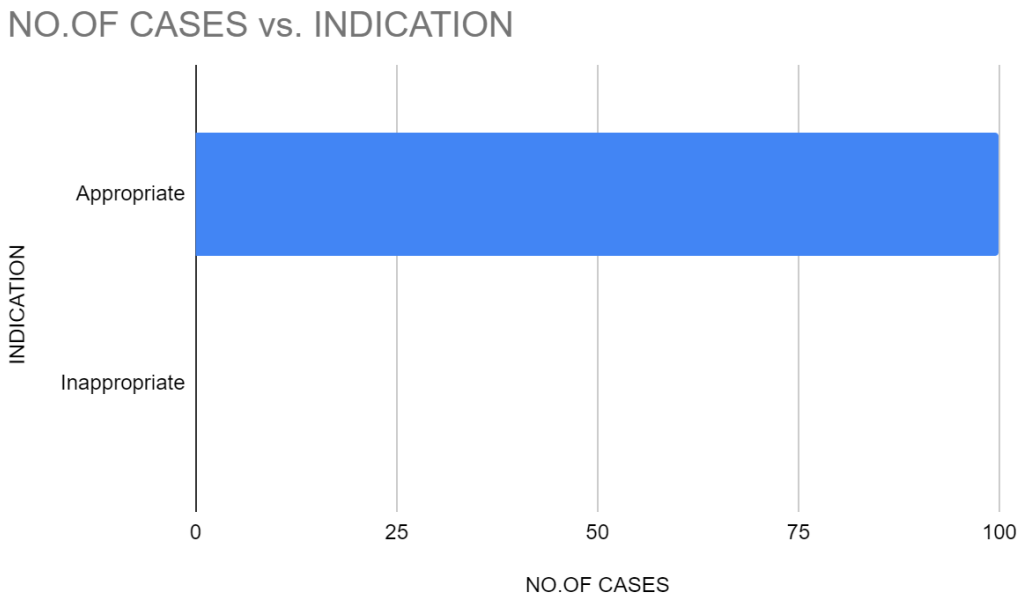

Fig. 10: Indication Accuracy.

DOSING ACCURACY

Table 11: Dosing Accuracy.

DOSE	NO. OF CASES
Right dose	100
Over dose	0
Under dose	0
Total	100

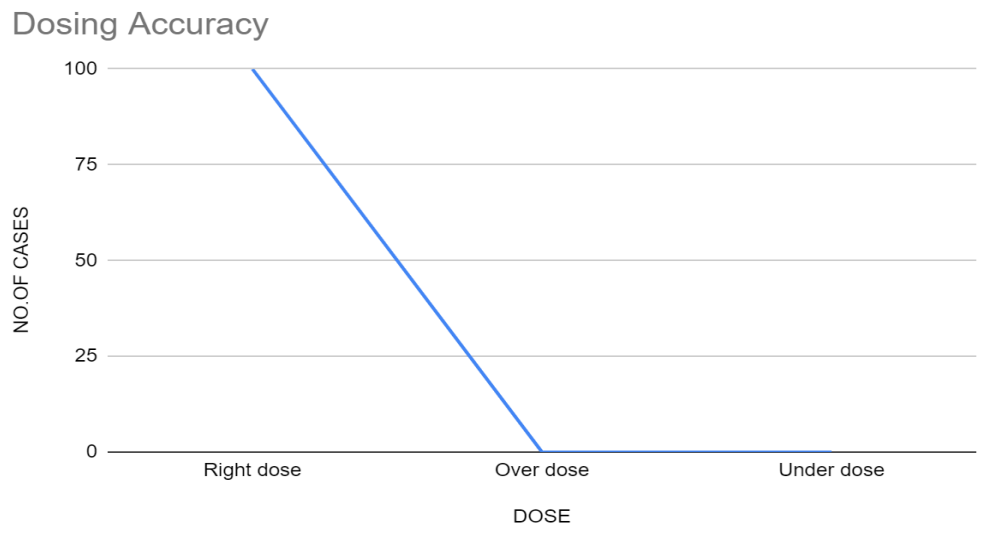

Fig. 11: Dosing Accuracy.

SUMMARY

- 39% of the 100 patients in the study are female, and 61% of the patients are male.
- Patients prescribed dapagliflozin were within the age range of 30 to 90 years.
- Dapagliflozin is predominantly prescribed within the age group of 50 to 70 years.
- Out of 100 patients, 61% have a family history of T2DM.
- The majority of patients are overweight, nearly 70%.
- Half of the patients in the study have co-morbidities, including conditions such as hypertension (HTN), hypothyroidism, myocardial infarction (MI), and diabetic retinopathy.
- The prescribing pattern in the study indicates that the majority of patients, accounting for 55%, are prescribed Udapa, followed by Dapefy at 25% and Dapanorm at 11%.
- A small percentage, specifically 5% of patients in the study, reported experiencing minor side effects such as dry mouth and increased urination. This suggests a generally favorable safety profile for dapagliflozin, with a low incidence of mild adverse reactions in the observed patient population.

CONCLUSION

- In this study, the prescription of Udapa was predominant, primarily attributed to its perceived low risk and cost-effectiveness.
- The study revealed that dapagliflozin effectively lowered blood glucose levels, presenting it as a clinically beneficial option and even economically affordable to patients.
- According to the study's findings, the patients did not experience any significant adverse events. However, minor side effects were observed in 5% of the study participants.

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